MYCOBACTERIUM TUBERCULOSIS DISEASE WITH HIV COINFECTION

(Updated January 10, 2011)

Panel's Recommendations:

- ***The treatment of active tuberculosis (TB) disease in patients with HIV infection should follow the same principles for persons without HIV infection (AI).***
- ***All HIV-infected patients with diagnosed active TB should be started on TB treatment immediately (AI).***
- ***All HIV-infected patients with diagnosed active TB should be treated with antiretroviral therapy (ART) (AI).***
- ***For patients with CD4 count <200 cells/mm^3, ART should be initiated within 2–4 weeks of starting TB treatment (AI).***
- ***For patients with CD4 count 200–500 cells/mm^3, the Panel recommends initiation of ART within 2–4 weeks, or at least by 8 weeks after commencement of TB therapy (AIII).***
- ***For patients with CD4 count >500 cells/mm^3, most Panel members also recommend starting ART within 8 weeks of TB therapy (BIII).***
- ***Despite pharmacokinetic drug interactions, a rifamycin should be included in regimens for patients receiving ART, with dosage adjustment if necessary (AII).***
- ***If a protease inhibitor (PI)-based regimen is used, rifabutin is the preferred rifamycin in HIV-infected patients with active TB disease due to its lower risk of substantial interactions with PIs (AII). Coadministration of rifampin and PIs (with or without ritonavir [RTV] boosting) is not recommended (AII).***
- ***Immune reconstitution inflammatory syndrome (IRIS) may occur after initiation of ART. Both ART and TB treatment should be continued while managing IRIS (AIII).***
- ***Treatment support, including directly observed therapy (DOT) of TB treatment, is strongly recommended for HIV-infected patients with active TB disease (AII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Terminology: In this section, the terms "HIV-infected with active TB disease" and "HIV/TB disease" are used synonymously to designate HIV-infected patients with active TB disease in need of TB treatment. "HIV/TB coinfection" is not used because the term can refer to either active TB or latent TB infection (LTBI) in the presence of HIV infection and may cause confusion.

Treatment of Active TB in HIV Patients

HIV infection significantly increases the risk of progression from latent to active TB disease. The CD4 cell count influences both the frequency and severity of active TB disease *[1-2]*. Active TB also negatively affects HIV disease. It may be associated with a higher HIV viral load and more rapid progression of HIV disease *[2-3]*.

Active pulmonary or extrapulmonary TB disease requires prompt initiation of TB treatment. The treatment of active TB disease in HIV-infected patients should follow the general principles for persons without HIV (**AI**). Treatment of drug-susceptible TB disease should include a standard regimen that consists of isoniazid (INH) + a rifamycin (rifampin or rifabutin) + pyrazinamide + ethambutol given for 2 months, followed by INH + a rifamycin for 4 to 7 months *[4]*. A more complete discussion of the diagnosis and treatment of TB disease and LTBI in HIV patients is available in the ***Guidelines for Preventing and Treating Opportunistic Infections in HIV-Infected Adults and Adolescents*** *[4]*.

All patients with HIV/TB disease should be treated with ART **(AI)**. Important issues related to the use of ART in patients with active TB disease include: (1) when to start ART, (2) significant pharmacokinetic drug interactions with rifamycins, (3) the additive toxicities associated with ARV and TB drugs, (4) the development of IRIS with TB after

ART initiation, and (5) the need for treatment support including DOT and the integration of HIV and TB care and treatment.

When to Start Antiretroviral Therapy

Patients Diagnosed with TB While Receiving ART

At the time TB treatment is initiated in patients receiving ART, the patient's ARV regimen should be assessed with particular attention to potential pharmacokinetic interactions with rifamycins (discussed below). The patient's regimen may need to be modified to permit use of the optimal TB treatment regimen.

Patients Receiving Treatment for Active TB but Not Yet on ART

When to initiate ART in patients with active TB has been the subject of differing recommendations based upon observational studies and expert opinion *[4-6]*. Two randomized controlled trials now provide some additional evidence regarding this issue. In these studies, concomitant administration of therapy for both TB disease and HIV infection resulted in significant reduction in HIV/TB disease mortality *[7-8].* The results of an ACTG trial will soon be available and may provide further guidance or support for recommendations concerning when to start ART in patients with active TB.

In the SAPIT study from South Africa, HIV-infected patients with smear-positive TB and CD4 counts <500 cells/mm^3 were randomized to one of three treatment arms: integrated therapy with ART initiated either during the first 4 weeks of TB therapy or after the second month (i.e., during the continuation phase of TB therapy) or sequential therapy with ART initiated after the conclusion of standard TB therapy. The sequential arm was stopped when an early analysis demonstrated a 55% reduction in mortality in the combined two integrated arms compared with the sequential therapy arm *[7]*. In the CAMELIA study from Cambodia *[8],* patients with CD4 counts <200 cells/mm^3 were randomized to initiate ART at 2 weeks or at 8 weeks of TB treatment. A 34% reduction in mortality was seen with ART initiation at 2 weeks compared with initiation at 8 weeks ($p = 0.002$). The populations in these two studies differed: the median CD4 count among SAPIT participants was 140–150 cells/mm^3; in the CAMELIA trial, the median CD4 count at entry was 25 cells/mm^3. Low CD4 count at study baseline predicted poorer survival in both studies. Both studies demonstrated excellent ART response: 90% and >95% of participants achieved suppressed HIV RNA (<400 copies/mL) at 12 months in the SAPIT study and CAMELIA trial, respectively. Although in both studies IRIS was more common in patients initiating ART earlier, the syndrome was not associated with mortality.

Based on the available data and the potential benefits of ART in patients with active TB, the Panel recommends the following:

- ***For patients with CD4 count <200 cells/mm^3, ART should be initiated within 2–4 weeks of starting TB treatment (AI).***
- ***For patients with CD4 count 200–500 cells/mm^3, the Panel recommends initiation of ART within 2–4 weeks, or at least by 8 weeks after commencement of TB therapy (AIII).***
- ***For patients with CD4 count >500 cells/mm^3, most Panel members also recommend starting ART within 8 weeks of TB therapy (BIII).***

ART should be started as early as feasible for all HIV-infected pregnant women with active TB, both for maternal health and for prevention of mother-to-child transmission (PMTCT) of HIV **(AIII)**. An augmented immune or inflammatory response in patients with some manifestations of TB, such as meningitis, pericarditis, or respiratory failure, might be life threatening. In these circumstances, delaying initiation of ART briefly beyond recommended intervals may be appropriate **(CIII)**.

Drug Interaction Considerations

A rifamycin is a crucial component for the treatment of drug-sensitive TB. However, both rifampin and rifabutin are inducers of the hepatic cytochrome P (CYP) 450 and uridine diphosphate gluconyltransferase (UGT) 1A1 enzymes and are associated with interactions with most ARV agents including all PIs, non-nucleoside reverse transcriptase

inhibitors (NNRTIs), maraviroc (MVC), and raltegravir (RAL). Rifampin is a strong enzyme inducer, leading to enhanced drug clearance and greater reduction in ARV drug exposure. Rifabutin, a weaker enzyme inducer, is an alternative to rifampin. Because rifabutin is a substrate of the CYP 450 enzyme system, its metabolism may be affected by the NNRTI or PI as discussed below. **Tables 15a and 15b** outline the magnitude of these interactions and provide dosing recommendations when rifamycins and selected ARV drugs are used concomitantly. After determining the drugs and doses to use, patients should be closely monitored to assure good control of both TB and HIV. Suboptimal HIV suppression or suboptimal response to TB treatment should prompt assessment of drug adherence, subtherapeutic drug levels (consider therapeutic drug monitoring [TDM]), and acquired drug resistance.

Rifamycins and NNRTIs

Rifampin induces metabolism of both nevirapine (NVP) *[9]* and efavirenz (EFV) *[10]* leading to reduced NNRTI drug exposure. The extent of induction is less pronounced with EFV than with NVP. Despite the interactions, some observational studies suggest that good virologic, immunologic, and clinical outcomes may be achieved with standard doses of either EFV *[11-12]* or NVP *[13-14]* when combined with rifampin.

Rifabutin does not significantly affect EFV and NVP drug exposure. Because both EFV and NVP can induce rifabutin metabolism, an increased rifabutin dose is recommended. Few data exist on the use of rifampin and etravirine (ETR); however, because rifampin is expected to induce ETR metabolism, concomitant use is not recommended. Rifabutin is recommended in this situation.

Rifamycins and PIs

Rifampin can significantly decrease PI drug exposure, despite ritonavir (RTV) boosting, with resultant risk of ART failure *[15-16]*. Some investigators had explored the use of an additional RTV dose or doubling PI doses in attempt to overcome rifampin's induction effect. However, a high rate of serious hepatotoxicity and significant gastrointestinal intolerance resulted in terminations of these studies *[15, 17-18]*. Therefore, coadministration of rifampin and PIs is **not recommended** (**AII**).

Because rifabutin has a less significant impact on the pharmacokinetics of RTV-boosted PIs, it is the preferred rifamycin to use with PI-based regimens **(AII)**. Both RTV-boosted and -unboosted PIs can inhibit rifabutin metabolism and the optimal dose of rifabutin is yet to be defined. Most PI manufacturers suggest rifabutin 150 mg every other day (instead of normal doses of 300 mg once daily). Lower than expected drug exposure *[19-20]* and acquired rifamycin resistance have been reported in HIV-infected patients who received PI-based regimens and intermittent doses of rifabutin *[19, 21]*. If available, TDM can be helpful in assessing the adequacy of rifabutin drug exposure.

Rifamycins and MVC or RAL

MVC is a substrate of CYP3A4 and rifampin can significantly reduce MVC concentration. If concomitant use is necessary, the MVC dose should be increased. Rifabutin may be an alternative rifamycin. (See **Table 15d** for recommended doses of MVC used with rifamycins.)

Rifampin, a strong UGT1A1 enzyme inducer, significantly accelerates the metabolism of RAL *[22]*. When used in combination with rifampin, the RAL dose should be increased to 800 mg twice daily. Rifabutin has minimal effect on RAL metabolism and may be more appropriate in this situation.

Anti-TB/ARV Toxicities

ARV agents and TB drugs, particularly INH, rifamycin, and pyrazinamide, can cause drug-induced hepatitis. These first-line TB drugs should still be used for treatment of active TB disease, even with coadministration of other potentially hepatotoxic drugs or in the presence of baseline liver disease **(AIII)**. Patients receiving drugs with potential hepatotoxicity should have frequent monitoring for clinical symptoms and signs of hepatitis and laboratory monitoring for hepatotoxicity. Peripheral neuropathy can occur with INH, didanosine (ddI), or stavudine (d4T) or may be a manifestation of HIV. All patients receiving INH should also receive supplemental pyridoxine to reduce peripheral

neuropathy. Patients should be monitored closely for signs of drug-related toxicities and receive alternatives to ddI or d4T.

IRIS with TB and ARV Agents

IRIS occurs in two forms, "unmasking" and "paradoxical." The mechanism is the same for both forms of IRIS: restoration of immune competence by administration of ARV agents, resulting in an exuberant host response to TB bacilli and/or antigens. Unmasking IRIS refers to the initial clinical expression of active TB occurring soon after ARV agents are started. Paradoxical IRIS refers to the worsening of TB clinical manifestations after ARV agents are started in patients who are receiving TB treatment. Severity of IRIS ranges from mild to severe to life threatening. IRIS has been reported in 8% to greater than 40% of patients starting ART after TB is diagnosed, although the incidence depends on the definition of IRIS and the intensity of monitoring *[23-24]*.

Predictors of IRIS include CD4 count <50 cells/mm^3, higher on-ART CD4 counts, high pre-ART and lower on-ART HIV viral loads, severity of TB disease, especially high pathogen burden, and less than 30-day interval between initiation of TB and HIV treatments. *[5, 25-29]*. Most IRIS in HIV/TB disease occurs within 3 months of the start of TB treatment. Delaying the start of ART for 2–8 weeks may reduce the incidence and severity of IRIS but must be weighed against the potential benefit of earlier ART in improving immune function and preventing progression of HIV disease and mortality.

Milder or moderately severe cases of IRIS can be managed symptomatically or treated with nonsteroidal inflammatory agents. More severe cases can be successfully treated with corticosteroids. A recent randomized, placebo-controlled trial demonstrated benefit of corticosteroid treatment as measured by decreasing days of hospitalization and Karnofsky performance score without adverse consequences *[30]*. In the presence of IRIS, neither TB therapy nor ART should be stopped because both therapies are necessary for the long-term health of the patient **(AIII)**.

Immune Reconstitution with ART: Conversion to Positive Tuberculin Skin Test (TST) and Interferon-Gamma (IFN-γ) Release Assay (IGRA)

Immune reconstitution with ART may result in unmasking LTBI (i.e., conversion of a previously negative TST to a positive TST or a positive IGRA for *Mycobacterium tuberculosis*-specific proteins). A positive IGRA, similar to a positive TST, is indicative of LTBI in the absence of evidence of active TB disease *[31]*. Because treatment for LTBI is indicated in the absence of evidence of active TB disease, clinicians should be aware of this phenomenon. Patients with a negative TST or IGRA and advanced HIV disease (i.e., CD4 count <200 cells/mm^3) should have a repeat TST or IGRA after initiation of ART and CD4 count increase to >200 cells/mm^3 *[32]* **(BII)**.

Caring for Patients with HIV and TB

Integration of diagnosis and treatment and/or close collaboration between TB and HIV clinicians, health care institutions, and public health programs are necessary in order to improve medication adherence and TB treatment completion rates, reduce toxicities, and maximize HIV outcomes in HIV-infected patients with active TB disease *[4]*. These patients should receive treatment support, including adherence counseling and DOT, corresponding to their needs **(AII)**. ART simplification or use of coformulated fixed-dose combinations may also be helpful to improve drug adherence.

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